Effects of Ketamine, Halothane, Enflurane, and Isoflurane on Systemic and Splanchnic Hemodynamics in Normovolemic and Hypovolemic Cirrhotic Rats

Bertrand Debaene, M.D.,* Gérard Goldfarb, M.D.,† Alain Braillon, M.D.,‡ Pierre Jolis, M.D.,§ Didier Lebrec, M.D.¶

The effects of ketamine, halothane, enflurane, and isoflurane on systemic and splanchnic hemodynamics in cirrhotic rats that were either normovolemic or hypovolemic following hemorrhage were characterized. Rats received at random either ketamine (30 mg/kg iv, 1.3 mg·kg⁻¹·min⁻¹ iv), halothane, enflurane, or isoflurane (1 MAC). Conscious rats were considered the control group. Four weeks before hemodynamic studies bile duct ligation was performed in all rats to induce cirrhosis. Hemodynamic measurements were performed using the radioisotope microsphere method 1 h after the onset of anesthesia and 30 min after hemorrhage. Anesthetized rat lungs were mechanically ventilated with room air. Before hemorrhage cardiac index was higher in conscious rats and in rats receiving isoflurane than in the other groups (P < 0.001). Hepatic arterial blood flow was similar in conscious rats and in those receiving isoflurane or halothane and was higher than in those receiving ketamine or enflurane. The lowest splanchnic and portal venous tributary blood flows were observed in rats receiving enflurane. After hemorrhage cardiac index was significantly less than before hemorrhage in all groups, except in rats receiving enflurane. After hemorrhage portal venous tributary blood flow decreased significantly in all groups except in enflurane group. During halothane and enflurane anesthesia hepatic arterial blood flow and hepatic arterial fraction of cardiac output decreased (P < 0.01) and they were maintained in the other groups. After hemorrhage hepatic arterial fraction of cardiac output in conscious rats was higher than in those receiving ketamine, halothane, or enflurane (P < 0.05) and was similar to those receiving isoflurane. Thus, halothane inhibited the increase of hepatic arterial blood flow, whereas it was maintained under isoflurane as in normals. Furthermore, in normovolemic cirrhotic rats hepatic arterial blood flow was preserved only during halothane and isoflurane. After hemorrhage among the agents and doses studied, isoflurane seems the most efficient for preserving splanchnic circulation in hypovolemic cirrhotic rats. (Key words: Anesthetics, intravenous ketamine. Anesthetics, volatile: enflurane; halothane; isoflurane. Liver: blood flow; cirrhosis. Species: rat.)

In patients with liver disease the anesthetic of choice remains unclear. An appropriate anesthetic agent should have at least three characteristics. First, it should have no hepatotoxicity because additional hepatic damage in these patients might provoke major liver failure. Second, it should have an extrahepatic elimination to limit impact of liver disease upon pharmacokinetic parameters. Finally, the anesthetic agent should have no effects or minor effects on hepatic blood flow in patients with hepatic blood flow alterations.1,2 In animals3,4 halothane, and to a lesser extent enflurane, induces more hepatocellular damage than isoflurane. Moreover, halothane decreases hepatic blood flow more than isoflurane.5,6 In normal animals compensatory increased hepatic arterial blood flow in response to a decrease in portal tributary blood flow (hepatic arterial buffer response) does not occur under halothane, whereas it is preserved under isoflurane.7 Thus, isoflurane should preserve hepatic oxygen supply better than halothane.8,9 The comparative effects of anesthetic agents on splanchnic circulation in cirrhotic animals have not yet been studied. In the present study we characterized the effects of ketamine, halothane, enflurane, and isoflurane on systemic and splanchnic hemodynamics in cirrhotic rats that were either normovolemic or hypovolemic following hemorrhage.

Materials and Methods

The type of experiments has been approved by the Agricultural Office, which is responsible in France for the application of the present European legislation. Seventy-five male Sprague-Dawley rats (Charles River, Saint-Aubin-lès-Elbeuf, France) were studied (mean body weight 308 ± 5 g). Cirrhosis was induced in all rats by common bile duct ligation—section.10 Under ether anesthesia the common bile duct was exposed through a midline abdominal incision, doubly ligated with 4-0 silk, and sectioned between the ligatures. The incision was then closed and the animal allowed to recover. Hemodynamic studies were performed 4 weeks after surgical procedure. Rats that had not overt macroscopic cirrhosis were rejected from the study before regional blood flow calculation. For the hemodynamic experiments rats were allowed free access to food and water until 14–16 h before study when food was withdrawn. Cirrhotic animals were divided into five groups based upon anesthetic exposure. Anesthetized cirrhotic rats received at random ketamine, halothane, enflurane, or isoflurane, whereas conscious cirrhotic animals were considered the control group.
Blood gas, arterial pressure, heart rate, cardiac output, and regional organ blood flows were determined in all rats. Before the hemodynamic study all rats received ether for catheterization of the left femoral artery, left femoral vein, and left ventricle via the right carotid artery, and a tracheostomy was performed (except in conscious rats). All incisions were closed with catgut after local application of 2% lidocaine gel, intended to minimize postoperative pain. Rats of the conscious group were then securely placed in a restraining apparatus and allowed to reawaken.

When vascular access was obtained, ether administration was discontinued. When animals began to recover, i.e., 10 min after the end of ether administration, anesthesia was started and the lungs were mechanically ventilated with room air (Vt = 1 ml · 100 g⁻¹ body weight, rate = 60 min⁻¹, PEEP = 0) using a small animal ventilator. Ketamine was administered as an iv bolus (30 mg/kg), followed by a continuous infusion at a rate of 1.5 mg · kg⁻¹ · min⁻¹ throughout the experiment. Halothane, enflurane, and isoflurane were continuously administered at 1 MAC concentration (1%, 2.2%, and 1.3% inspired for halothane, enflurane, and isoflurane, respectively). In the three latter groups and in conscious rats, saline was infused in the femoral vein at the rate of 1.2 ml/h that was equal to the flow rate received by rats anesthetized with ketamine. Heart rate, mean arterial pressure, and rectal temperature (maintained at 37° C by heating lamps) were continuously monitored. Inspired fraction of halogenated anesthetic was continuously measured with an infrared analyzer (Norma™, Datex, Helsinki, Finland). The protocol consisted of a 1-h period of stable anesthesia (no anesthesia in conscious animals) after surgical preparation followed by withdrawal of 20% of the estimated blood volume (shed blood volume = 1.25 ml · 100 g⁻¹ body weight) gradually over a 10-min period. Preliminary studies showed that this blood volume depletion was the maximal hemorrhage tolerable in anesthetized cirrhotic rats. Arterial P<sub>O</sub>2, P<sub>CO</sub>2, pH, heart rate, mean arterial pressure (MAP), cardiac index, and regional blood flows were measured before and 30 min after hemorrhage. Blood gas analysis was performed using a standard blood gas analyzer (CORNING 170 pH/blood gas analyzer™, Ciba Corning Diagnostics Corp., Melfield, CT).

Cardiac output and regional blood flows were determined by the radioactive microspheres method. A precounuted aliquot of approximately 60,000 15-μm diameter 141Ce or 113Sn labeled microspheres with a specific activity of 10 mCi/g was ultrasonically agitated. This was then injected into the ventricular catheter and flushed with 1 ml of physiologic saline over 45 s. Beginning 5 s before the injection the reference sample from the femoral artery catheter was withdrawn into a motor-driven syringe at 1 ml/min for 1 min.

Animals were then killed with iv KCl and individual organs dissected out. Radioactivity in each organ and the reference blood sample were counted by a gamma scintillation counter (Compteur Gamma 4000, Intertechnique, Plaisir, France). Adequate microsphere mixing was assured by a difference lower than 10% between left and right kidney; animals failing this requirement were rejected from analysis.

Cardiac output (CO) was calculated by the following formula:

\[
\text{CO (ml/min)} = \frac{\text{injected radioactivity (cpm)}}{\text{reference blood sample radioactivity (cpm)}} \times 1 \text{ (ml/min)}
\]

Cardiac index (CI) was derived by the following formula:

\[
\text{Cl (ml · min⁻¹ · 100 g⁻¹ body weight)} = \frac{\text{CO}}{\text{body weight (g)}} \times 100
\]

Total peripheral resistance (TPR) was calculated by the following formula:

\[
\text{TPR (dyne · s · cm⁻5)} = \frac{\text{MAP (mmHg) \times 80}}{\text{CO (ml/min)}} \times 10^3
\]

Regional blood flows were calculated by the following formula:

\[
\text{organ blood flow (ml/min)} = \frac{\text{organ radioactivity (cpm) \times CO (ml/min)}}{\text{injected radioactivity (cpm)}}
\]

Percent distribution of cardiac output was calculated as follows:

\[
\frac{\text{organ radioactivity (cpm)}}{\text{injected radioactivity (cpm)}}
\]

Portal venous tributary blood flow was calculated as the sum of stomach, intestine, colon, spleen, and mesentery with pancreas blood flows. Splanchnic blood flow was calculated as the sum of portal venous tributary and hepatic arterial blood flows.

**Statistical Analysis**

Results were expressed as mean ± SEM. Statistical analysis was performed using a Wilcoxon test to compare values before and after hemorrhage within each group. One-way analysis of variance and the Scheffe F test were used for multiple comparisons among groups before and after hemorrhage. The same tests were used to compare variations of the results observed after hemorrhage among groups. P < 0.05 was set as the significance level.
Results

Results concern 40 rats. The initial number of rats was 75. Fifteen rats died after the bile duct ligation section but before hemodynamic studies. Twelve rats were not included because they did not develop overt macroscopic cirrhosis. They were rejected at necropsy before regional blood flow calculation. Eight other rats were deleted because of microsphere mixing impairment. The final number of cirrhotic rats in each group was 8.

Before Hemorrhage

Cardiac index was significantly higher during isoflurane anesthesia and in conscious rats than during administration of the other anesthetic agents. Mean arterial pressure was not different among the four groups of anesthetized rats. It was significantly higher in conscious rats than in anesthetized rats. There were no significant differences among the five groups for heart rate. Total peripheral resistance was significantly higher in rats receiving enflurane than in those receiving ketamine, halothane, or isoflurane \((P < 0.01)\). \(\text{PaO}_2\) was significantly higher in conscious rats than in anesthetized rats. \(\text{PaCO}_2\) was significantly lower in conscious rats than those receiving ketamine. However, \(\text{PaCO}_2\) and \(\text{PaO}_2\) were similar in the four groups of anesthetized rats (Table 1).

Splanchnic blood flow was significantly higher in rats receiving isoflurane than in rats receiving enflurane \((P < 0.01)\), but it was not different between conscious rats and rats receiving halothane or isoflurane. Hepatic arterial blood flow was significantly less in animals receiving ketamine or enflurane than in those receiving halothane or isoflurane and in conscious rats \((P < 0.001)\) (Table 2). Hepatic arterial blood flow was not significantly different between conscious rats and those receiving isoflurane or halothane. The splanchnic fraction of cardiac output was significantly less in rats receiving ketamine than in animals receiving halothane or isoflurane \((P < 0.01)\). Splanchnic fraction of cardiac output was similar in rats receiving halothane, enflurane, or isoflurane and in conscious rats. Hepatic arterial fraction of cardiac output was not significantly different among the five groups (Table 3).

After Hemorrhage

After hemorrhage cardiac index was significantly less in all rats than values measured before hemorrhage except for rats receiving enflurane. In conscious rats mean arterial pressure was significantly higher than in all anesthetized rats. It was significantly higher in rats receiving ketamine or isoflurane than in those receiving halothane or enflurane \((P < 0.05)\). Mean arterial pressure did not change in rats receiving isoflurane, but it was significantly lower than before hemorrhage in animals receiving ketamine, halothane, and enflurane. There were no significant differences among these last three groups for the decrease in mean arterial pressure. The lowest mean arterial pressure after hemorrhage was observed in rats receiving halothane or enflurane. Heart rate was unchanged in rats receiving halothane, enflurane, or isoflurane, but it was significantly lower than values measured before hemorrhage in animals receiving ketamine.

### Table 1. Systemic Hemodynamics and Arterial Blood Gas Values in Cirrhotic Rats before and after Hemorrhage

<table>
<thead>
<tr>
<th>Condition</th>
<th>G (ml·min⁻¹·100 g body weight⁻¹)</th>
<th>K (mmHg)</th>
<th>H (mmHg)</th>
<th>E (mmHg)</th>
<th>I (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>N 69.3 ± 5.9†</td>
<td>52.9 ± 3.2</td>
<td>53.9 ± 4.2</td>
<td>44.6 ± 2.4</td>
<td>65.9 ± 2.9†</td>
</tr>
<tr>
<td></td>
<td>HE 36.9 ± 5.1*</td>
<td>44.2 ± 2.8*</td>
<td>45.4 ± 3.6*</td>
<td>35.9 ± 2.8</td>
<td>51.9 ± 5.2*</td>
</tr>
<tr>
<td>MAP</td>
<td>N 99.5 ± 2.4††</td>
<td>78.7 ± 3.8</td>
<td>72.1 ± 2.4</td>
<td>74.3 ± 2.5</td>
<td>82.5 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>HE 104.1 ± 5.0††</td>
<td>73.1 ± 4.1††</td>
<td>58.9 ± 3.8†</td>
<td>58.3 ± 2.6†</td>
<td>77.0 ± 3.9†</td>
</tr>
<tr>
<td>HR</td>
<td>N 387 ± 15</td>
<td>351 ± 21</td>
<td>321 ± 10</td>
<td>334 ± 7</td>
<td>358 ± 16</td>
</tr>
<tr>
<td></td>
<td>HE 430 ± 9.5*</td>
<td>325 ± 14*</td>
<td>330 ± 16</td>
<td>352 ± 8</td>
<td>380 ± 9†</td>
</tr>
<tr>
<td>TPR</td>
<td>N 41.5 ± 3.1</td>
<td>38.1 ± 2.8</td>
<td>39.2 ± 2.8</td>
<td>40.0 ± 2.8*</td>
<td>36.4 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>HE 87.5 ± 11.8††</td>
<td>42.3 ± 3.4</td>
<td>37.7 ± 3.1</td>
<td>48.1 ± 3.2</td>
<td>46.6 ± 7.5</td>
</tr>
<tr>
<td>(\text{PaO}_2) (mmHg)</td>
<td>N 98.9 ± 4.8†</td>
<td>68.7 ± 3.1</td>
<td>69.6 ± 4.4</td>
<td>80.8 ± 5.6</td>
<td>76.3 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>HE 97.2 ± 6.0*</td>
<td>72.5 ± 3.0</td>
<td>61.4 ± 5.0</td>
<td>60.3 ± 3.9*</td>
<td>70.2 ± 4.3</td>
</tr>
<tr>
<td>(\text{PaCO}_2) (mmHg)</td>
<td>N 26.5 ± 1.9**</td>
<td>34.6 ± 1.3</td>
<td>30.8 ± 1.3</td>
<td>31.9 ± 1.4</td>
<td>30.7 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>HE 23.8 ± 1.9††</td>
<td>38.5 ± 1.9*</td>
<td>37.9 ± 2.8*</td>
<td>35.9 ± 2.1*</td>
<td>37.7 ± 2.1*</td>
</tr>
<tr>
<td>(\rho H)</td>
<td>N 7.44 ± 0.01</td>
<td>7.39 ± 0.02</td>
<td>7.30 ± 0.02</td>
<td>7.38 ± 0.01</td>
<td>7.43 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>HE 7.39 ± 0.03‡‡</td>
<td>7.36 ± 0.02</td>
<td>7.30 ± 0.03*</td>
<td>7.37 ± 0.02*</td>
<td>7.35 ± 0.01*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

\(\text{CI} = \text{cardiac index; MAP = mean arterial pressure; HR = heart rate; TPR = total peripheral resistance; G = conscious; K = ketamine; H = halothane; E = enflurane; I = isoflurane. N = normovolemic; HE = 30 min after hemorrhage.}

\* Significantly different from normovolemic value \((P < 0.05)\).

\† Significantly different from anesthetized rats \((P < 0.001)\).

\‡ Significantly different from rats receiving ketamine, halothane, and enflurane \((P < 0.001)\).

\§ Significantly different from rats receiving ketamine, halothane, and isoflurane \((P < 0.01)\).

\‖ Significantly different from rats receiving ketamine and halothane \((P < 0.001)\).

\* Significantly different from rats receiving ketamine \((P < 0.01)\).

\†† Significantly different from rats receiving enflurane and halothane \((P < 0.05)\).

\‡‡ Significantly different from rats receiving enflurane \((P < 0.001)\).
### Table 2. Splanchnic Hemodynamics in Cirrhotic Rats before and after Hemorrhage

<table>
<thead>
<tr>
<th>Condition</th>
<th>C (ml/min-1 · g tissue weight-1)</th>
<th>K (ml/min-1 · g tissue weight-1)</th>
<th>H (ml/min-1 · g tissue weight-1)</th>
<th>E (ml/min-1 · g tissue weight-1)</th>
<th>I (ml/min-1 · g tissue weight-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>N 0.88 ± 0.12</td>
<td>0.78 ± 0.08</td>
<td>0.70 ± 0.09</td>
<td>0.77 ± 0.11</td>
<td>1.07 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>HE 0.32 ± 0.10*</td>
<td>0.62 ± 0.11*</td>
<td>0.33 ± 0.04*</td>
<td>0.41 ± 0.08*</td>
<td>0.48 ± 0.11*</td>
</tr>
<tr>
<td>Stomach</td>
<td>N 1.87 ± 0.29†</td>
<td>1.30 ± 0.32**</td>
<td>0.74 ± 0.13</td>
<td>0.50 ± 0.05</td>
<td>1.12 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>HE 0.83 ± 0.36*</td>
<td>0.85 ± 0.12</td>
<td>0.67 ± 0.08</td>
<td>0.42 ± 0.04</td>
<td>0.90 ± 0.18</td>
</tr>
<tr>
<td>Intestine</td>
<td>N 2.91 ± 0.74</td>
<td>2.87 ± 0.35</td>
<td>3.23 ± 0.19</td>
<td>2.49 ± 0.21</td>
<td>3.15 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>HE 1.36 ± 0.23**†</td>
<td>1.64 ± 0.28</td>
<td>2.44 ± 0.18*</td>
<td>2.21 ± 0.23</td>
<td>2.45 ± 0.35*</td>
</tr>
<tr>
<td>Colon</td>
<td>N 1.79 ± 0.56</td>
<td>1.54 ± 0.25</td>
<td>1.37 ± 0.19</td>
<td>0.84 ± 0.08</td>
<td>1.37 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>HE 0.68 ± 0.10*</td>
<td>1.10 ± 0.12</td>
<td>1.11 ± 0.13*</td>
<td>0.79 ± 0.07</td>
<td>1.07 ± 0.18</td>
</tr>
<tr>
<td>Mesentery-pancreas</td>
<td>N 1.79 ± 0.15</td>
<td>1.34 ± 0.13</td>
<td>1.29 ± 0.26</td>
<td>0.78 ± 0.09</td>
<td>1.96 ± 0.22</td>
</tr>
<tr>
<td>PVT (ml/min-1 · 100 g body weight)</td>
<td>N 10.93 ± 1.67</td>
<td>8.67 ± 0.71</td>
<td>9.64 ± 0.76</td>
<td>6.55 ± 0.47</td>
<td>10.96 ± 0.85</td>
</tr>
<tr>
<td></td>
<td>HE 4.67 ± 0.99*</td>
<td>6.75 ± 0.64*</td>
<td>6.75 ± 0.69*</td>
<td>5.57 ± 0.57</td>
<td>7.25 ± 1.15*</td>
</tr>
<tr>
<td>Liver</td>
<td>N 1.07 ± 0.15</td>
<td>0.58 ± 0.10§</td>
<td>1.16 ± 0.12</td>
<td>0.66 ± 0.07§</td>
<td>1.24 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>HE 0.91 ± 0.13</td>
<td>0.64 ± 0.08</td>
<td>0.76 ± 0.13*</td>
<td>0.47 ± 0.07*</td>
<td>0.96 ± 0.11**</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>N 18.58 ± 2.40</td>
<td>13.72 ± 1.46</td>
<td>17.47 ± 1.46</td>
<td>11.75 ± 0.65</td>
<td>19.58 ± 0.89**</td>
</tr>
<tr>
<td></td>
<td>HE 11.09 ± 1.80*</td>
<td>12.13 ± 1.04</td>
<td>11.81 ± 1.05*</td>
<td>9.24 ± 0.93</td>
<td>13.88 ± 1.45*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Portal venous tributary (PVT) blood flow is equal to the sum of spleen, stomach, intestine, colon, and mesentery—pancreas blood flows. Liver blood flow is equal to hepatic arterial flow. Splanchnic blood flow is equal to the sum of portal venous tributary and hepatic arterial blood flows. G = conscious; K = ketamine; H = halothane; E = enflurane; I = isoflurane; N = normovolemic; HE = 30 min after hemorrhage.

* Significantly different from normovolemic value ($P < 0.05$).
† Significantly different from anesthetized rats ($P < 0.01$).
‡ Significantly different from rats receiving halothane and enflurane ($P < 0.001$).
§ Significantly different from conscious rats and rats receiving halothane and isoflurane ($P < 0.001$).
¶ Significantly different from conscious rats and rats receiving isoflurane ($P < 0.001$).
** Significantly different from rats receiving enflurane ($P < 0.01$).

### Table 3. Portal Venous Tributary, Hepatic Arterial, and Splanchnic Blood Flows in the Cirrhotic Rats before and after Hemorrhage as a Percentage of Cardiac Output

<table>
<thead>
<tr>
<th>Condition</th>
<th>C (ml/min-1 · g tissue weight-1)</th>
<th>K (ml/min-1 · g tissue weight-1)</th>
<th>H (ml/min-1 · g tissue weight-1)</th>
<th>E (ml/min-1 · g tissue weight-1)</th>
<th>I (ml/min-1 · g tissue weight-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVT</td>
<td>N 14.07 ± 1.64</td>
<td>16.29 ± 0.61</td>
<td>17.88 ± 1.58</td>
<td>15.26 ± 2.07</td>
<td>16.72 ± 1.32</td>
</tr>
<tr>
<td></td>
<td>HE 10.15 ± 1.98*</td>
<td>15.32 ± 1.04</td>
<td>14.85 ± 1.19*</td>
<td>14.44 ± 2.08</td>
<td>13.46 ± 1.05*</td>
</tr>
<tr>
<td>Liver</td>
<td>N 10.82 ± 1.05</td>
<td>9.26 ± 1.18</td>
<td>14.60 ± 1.52</td>
<td>11.81 ± 1.49</td>
<td>13.18 ± 1.58</td>
</tr>
<tr>
<td></td>
<td>HE 17.68 ± 1.53**†</td>
<td>12.01 ± 1.21*</td>
<td>11.25 ± 1.68*</td>
<td>10.57 ± 1.68*</td>
<td>13.41 ± 1.48</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>N 26.38 ± 1.55</td>
<td>25.54 ± 1.47</td>
<td>32.49 ± 1.17*</td>
<td>26.63 ± 1.69</td>
<td>29.90 ± 1.33*</td>
</tr>
<tr>
<td></td>
<td>HE 29.55 ± 1.65</td>
<td>25.41 ± 1.49</td>
<td>26.08 ± 0.96*</td>
<td>26.13 ± 2.81</td>
<td>26.87 ± 1.20*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Portal venous tributary (PVT) flow is equal to the sum of percentage of cardiac output of the spleen, stomach, intestine, colon, and mesentery—pancreas; liver is equal to the percentage of cardiac output of the hepatic artery; splanchnic is equal to the sum of percentage of cardiac output of the portal venous tributary and the liver.

C = conscious; K = ketamine; H = halothane; E = enflurane; I = isoflurane; N = normovolemic; HE = 30 min after hemorrhage.
† Significantly different from normovolemic value ($P < 0.05$).
* Significantly different from rats receiving ketamine, halothane, and enflurane ($P < 0.05$).
‡ Significantly different from rats receiving ketamine ($P < 0.01$).
significantly higher than in rats receiving ketamine, halothane, or enflurane, whereas it was not different from rats receiving isoflurane (table 3).

Extrasplanchnic organ blood flows measured before and after hemorrhage are presented in table 4.

Discussion

The effects of isoflurane, halothane, enflurane, and ketamine on systemic and splanchnic hemodynamics have not been studied in cirrhotic animals. The present study showed that anesthetic agents have different effects on both systemic and splanchnic circulations in cirrhotic rats both before or after hemorrhage.

In these animals biliary cirrhosis was induced by bile duct ligation–section as previously described.17,18 Rats developed intrahepatic portal hypertension10 and liver failure19 similar to those in which cirrhosis is induced by CCl4 intoxication.20 Moreover, hemodynamic alterations observed in cirrhotic rats are similar to those observed in cirrhotic patients; they both have systemic and splanchnic hyperemia.21,22

Before the onset of administration of anesthetic agents, vascular access and tracheostomy were performed during a 30-min period under light ether anesthesia. The elimination of ether is slower than that of other volatile anesthetic agents.23 An effect of ether on hemodynamics seems doubtful for two reasons: 1) the administration of ether was intermittent with a light level of anesthesia; and 2) the hemodynamic measurements were performed 1 h after the end of ether anesthesia. Moreover, because anesthetic agents were continuously administered for 1 h before the first series of measurements, it can be assumed that a steady state level of anesthesia was obtained in all animals.24 Both ketamine and inhalation anesthesia offered stable conditions of anesthesia with loss of corneal and righting reflexes. In all anesthetized rats there was no response to tail clamping.

The lungs of all anesthetized rats were mechanically ventilated because anesthetic agents decrease alveolar ventilation. All anesthetized rats were studied in the same condition of mechanical ventilation. Among these four groups there were no differences in the values of PaCO2 either before or after hemorrhage. After hemorrhage, 100 min after the onset of mechanical ventilation, the PaCO2 of all anesthetized rats was slightly but significantly increased. The common effect of hypercarbia is an increased splanchnic blood flow.25,26 In the present study the increase in PaCO2 had no hemodynamic effects because PaCO2 did not reach a vasoactive value27 and remained in the normal range for rats.28 The values of PaCO2 might appear unusually low in our cirrhotic conscious rats. However, these values of PaCO2 were similar to those obtained by Seyde and Longnecker in rats without liver disease.7 We did not believe that the low PaCO2 values in conscious rats could be attributed to postoperative discomfort only. Incisions were infiltrated with 2% lidocaine gel prior to closure. Moreover, normal PaCO2 in awake rats is not well defined, ranging from 22 to 40 mmHg.

The effects of mechanical ventilation with intermittent positive pressure (IPPV) on splanchnic blood flow has not been well documented. Most of the studies have compared the effects of different techniques of mechanical ventilation, i.e., zero end-expiratory pressure versus PEEP. However, it has been shown that in animals anesthetized with barbiturates, the onset of IPPV decreases hepatic arterial blood flow.29 In this study portal venous blood flow was not measured. We cannot eliminate a role of mechanical ventilation in the differences observed in splanchnic hemodynamics between anesthetized and conscious rats. However, it is noteworthy that there were no differences in hepatic arterial blood flow values between conscious rats and rats anesthetized with halothane or isoflurane.

In anesthetized cirrhotic rats normovolemic hemodynamic values were different from those previously observed in normal rats receiving the same anesthetic agents.7 Cardiac index was higher and mean arterial pressure and total peripheral resistance were lower in cirrhotic rats than in normals. The circulatory changes have previously been reported in animals30 and in patients with cirrhosis.1

In cirrhotic rats as in normals receiving isoflurane, cardiac index was similar to that observed in conscious ani-

### Table 4. Coronary and Renal Blood Flows in Cirrhotic Rats before and after Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>K</th>
<th>H</th>
<th>E</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart (ml·min⁻¹·g tissue weight⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7.89 ± 1.49</td>
<td>5.17 ± 0.62</td>
<td>6.38 ± 1.11</td>
<td>4.28 ± 0.55</td>
<td>8.58 ± 1.67</td>
</tr>
<tr>
<td>HE</td>
<td>7.87 ± 1.03</td>
<td>5.77 ± 0.54</td>
<td>7.11 ± 1.16</td>
<td>5.86 ± 0.73</td>
<td>11.57 ± 1.99†</td>
</tr>
<tr>
<td><strong>Kidney (ml·min⁻¹·g tissue weight⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20.68 ± 2.78‡</td>
<td>12.18 ± 0.43</td>
<td>17.01 ± 1.34</td>
<td>14.95 ± 1.74</td>
<td>19.93 ± 2.19§</td>
</tr>
<tr>
<td>HE</td>
<td>12.37 ± 1.62*</td>
<td>15.80 ± 0.96</td>
<td>13.46 ± 1.07*</td>
<td>10.99 ± 0.72</td>
<td>15.33 ± 1.57</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

C = conscious; K = ketamine; H = halothane; E = enflurane; I = isoflurane; N = normovolemia; HE = 30 min after hemorrhage.

* Significantly different from normovolemic value (P < 0.05).
† Significantly different from conscious rats and rats receiving ketamine, halothane, and enflurane (P < 0.01).
‡ Significantly different from rats receiving ketamine and enflurane (P < 0.01).
§ Significantly different from rats receiving ketamine (P < 0.05).
mals. Halothane and enflurane both significantly decreased cardiac index. During ketamine cardiac index decreased in cirrhotic rats, whereas it is increased in normal rats or in humans. These results during ketamine suggest that the sympathomimetic effects of this agent could not occur in cirrhotic rats because they have an already increased sympathetic tone and decreased sensitivity to catecholamines and vasoconstrictors. Thus, the direct negative inotropic effects of ketamine may have acted in these animals.

Before hemorrhage no significant differences in splanchnic blood flow were found among rats receiving isoflurane, halothane, or ketamine. This may be due, at least in part, to the wide range of splanchnic blood flow values observed in this model of cirrhosis. However, splanchnic blood flow was significantly less in rats receiving enflurane than in rats receiving isoflurane and could be related to the lower cardiac index in rats receiving enflurane. Hepatic arterial blood flow was significantly less in rats receiving ketamine or enflurane than in those receiving halothane and isoflurane. The vasocostrictive effect of ketamine on hepatic arterial blood flow has previously been observed in animals without liver disease. Hepatic arterial blood flow under isoflurane or halothane was similar in cirrhotic rats. These findings are similar to those previously reported by Seyde and Longnecker in rats without liver disease. In the present study portal tributary blood flow was similar in the four groups of anesthetized cirrhotic rats. In contrast, it has been reported in rats without liver disease that portal tributary blood flow differs depending upon which anesthetic is being administered. During isoflurane it was higher than during halothane and lower than during ketamine. The different results of portal tributary blood flow between normals and cirrhotic rats could be explained by the absence of vasoactive response in rats with cirrhosis.

Hemorrhage induced systemic and splanchnic hemodynamic alterations in all rats. During ketamine or halothane both cardiac index and mean arterial pressure decreased, whereas cardiac index alone decreased in conscious rats and in those receiving isoflurane. In anesthetized cirrhotic rats total peripheral resistance did not increase to maintain mean arterial pressure after hemorrhage. In contrast, a significant increase in total peripheral resistance occurred in conscious animals, although it did not reach a significant level during isoflu- rane. These differences in response to acute hypovolemia between ketamine and halothane and isoflurane are similar to those observed with same anesthetic agents in normal rats.

In conscious normal animals a decrease in portal tributary blood flow induces a vasodilation of the hepatic artery ensuing an increase in hepatic arterial blood flow. The hepatic arterial buffer response did not occur with all anesthetic agents. Cirrhotic rats receiving halothane or isoflurane showed a similar decrease in portal tributary blood flow. However, the response of hepatic arterial blood flow was different. Under halothane hepatic arterial blood flow decreased after hemorrhage, whereas it was maintained during isoflurane. The inhibition of the hepatic arterial buffer response during halothane has already been demonstrated in normal rats. Moreover, after hemorrhage in cirrhotic rats hepatic fraction of cardiac output decreased during halothane or enflurane but not during isoflurane. Both portal tributary and hepatic arterial blood flows contribute to hepatic oxygen supply, but it appears that the oxygen supply to the liver depends to a large extent on hepatic arterial blood flow. After hemorrhage hepatic arterial blood flow was higher under isoflurane than under the other agents and was similar to that observed in conscious rats. Thus, in cirrhotic rats isoflurane seems to better preserve hepatic oxygen supply than the other agents, and this effect has already been observed in normal rats.

Although coronary blood flow tended to be higher during isoflurane than the other anesthetic agents even before hemorrhage, the difference only reached the significant level after hemorrhage. This is in accordance with the findings of Seyde and Longnecker and is probably related to the vasodilating properties of isoflurane. In contrast, with rats without liver disease isoflurane better preserved renal blood flow than ketamine in normovolemic cirrhotic rats.

In conclusion, ketamine and halogenated agents affected systemic and splanchnic circulation in cirrhotic rats. The variations of systemic and splanchnic hemodynamics induced by hemorrhage were similar to those observed in normal rats except under ketamine. All anesthetic agents had the same effect on portal tributary blood flow but acted differently on hepatic arterial blood flow. In anesthetized normovolemic cirrhotic rats hepatic arterial blood flow was preserved only with halothane and isoflurane. After hemorrhage hepatic arterial blood flow was maintained with isoflurane, whereas it decreased with halothane. Therefore, among the agents studied, isoflurane seems the most efficient for preserving splanchnic circulation in hypovolemic cirrhotic rats.

References


